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Abstract: The aim of the present study was to assess the potential effects of intermittent Universal Mobile Telecommunications System electromagnetic fields (UMTS-EMF) on blood circulation in the human head (auditory region) using near-infrared spectroscopy (NIRS) on two different timescales: short-term (effects occurring within 80 s) and medium-term (effects occurring within 80 s to 30 min). For the first time, we measured potential immediate effects of UMTS-EMF in real-time without any interference during exposure. Three different exposures (sham, 0.18 W/kg, and 1.8 W/kg) were applied in a controlled, randomized, crossover, and double-blind paradigm on 16 healthy volunteers. In addition to oxy-, deoxy-, and total haemoglobin concentrations ([O(2) Hb], [HHb], and [tHb], respectively), the heart rate (HR), subjective well-being, tiredness, and counting speed were recorded. During exposure to 0.18 W/kg, we found a significant short-term increase in Δ[O(2) Hb] and Δ[tHb], which is small (17%) compared to a functional brain activation. A significant decrease in the medium-term response of Δ[HHb] at 0.18 and 1.8 W/kg exposures was detected, which is in the range of physiological fluctuations. The medium-term ΔHR was significantly higher (+1.84 bpm) at 1.8 W/kg than for sham exposure. The other parameters showed no significant effects. Our results suggest that intermittent exposure to UMTS-EMF has small short- and medium-term effects on cerebral blood circulation and HR.

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Assessment of Intermittent UMTS Electromagnetic Field Effects on Blood Circulation in the Human Auditory Region Using a Near-Infrared System

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The aim of the present study was to assess the potential effects of intermittent Universal Mobile Telecommunications System electromagnetic fields (UMTS-EMF) on blood circulation in the human head (auditory region) using near-infrared spectroscopy (NIRS) on two different time-scales: short-term (effects occurring within 80 s) and medium-term (effects occurring within 80 s to 30 min). For the first time, we measured potential immediate effects of UMTS-EMF in real-time without any interference during exposure. Three different exposures (sham, 0.18 W/kg, and 1.8 W/kg) were applied in a controlled, randomized, crossover, and double-blind paradigm on 16 healthy volunteers. In addition to oxy-, deoxy-, and total haemoglobin concentrations ([O_2Hb],[HHb], and [tHb], respectively), the heart rate (HR), subjective well-being, tiredness, and counting speed were recorded. During exposure to 0.18 W/kg, we found a significant short-term increase in Δ[O_2Hb] and Δ[tHb], which is small ($\approx$17%) compared to a functional brain activation. A significant decrease in the medium-term response of Δ[HHb] at 0.18 and 1.8 W/kg exposures was detected, which is in the range of physiological fluctuations. The medium-term ΔHR was signifi-cantly higher (+1.84 bpm) at 1.8 W/kg than for sham exposure. The other parameters showed no significant effects. Our results suggest that intermittent exposure to UMTS-EMF has small short-and medium-term effects on cerebral blood circulation and HR. Bioelectromagnetics 33:40–54, 2012. © 2011 Wiley Periodicals, Inc.

Key words: blood circulation; heart rate; human studies

INTRODUCTION

The growing use of mobile phones in today's communication increases the duration that individuals are exposed to radiofrequency electromagnetic fields (RF-EMF). To assess the potential effects of RF-EMF exposure, several studies have been performed for different exposed biosystems ranging from cells to humans [Vecchia et al., 2009]. Many studies focused on the head, since it is the part of the body receiving the highest RF-EMF dose during mobile phone calls [Valentini et al., 2007]. Significant effects of Global System for Mobile Communications (GSM) RF-EMF on sleep EEG [Borbely et al., 1999; Huber et al., 2000, 2002; Regel et al., 2007b] and waking EEG [Huber et al., 2002; Curcio et al., 2005; Regel et al., 2007a; Croft et al., 2008] where shown, while other studies found no effects [Röschke and Mann, 1997; Hietanen et al., 2000;

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Hinrichs and Heinze, 2006; Kleinlogel et al., 2008]. Using positron emission tomography (PET), regional cerebral blood flow (rCBF) was significantly increased 30 min after exposure to GSM RF-EMF [Huber et al., 2002, 2005], but decreased for other locations [Aalto et al., 2006]. Another study measured a decrease in rCBF, although this was probably a spurious auditory effect [Haarala et al., 2003]. Only one study for Universal Mobile Telecommunications System electromagnetic fields (UMTS-EMF) observed no changes in rCBF [Mizuno et al., 2009].

PET has a low time resolution (15–30 min) and is, therefore, only suited to study slow effects. Another technique to measure blood concentration and oxygenation changes with a much higher temporal resolution (≈100 Hz) is near-infrared spectroscopy (NIRS). Near-infrared light (650–950 nm) penetrates tissue relatively deeply, i.e., at least 2.5 cm [Toronov et al., 2001b], which enables researchers to study the brain [Wolf et al., 2007]. Using two wavelengths, concentration changes are measured in oxy-, deoxy-, and total haemoglobin ($\Delta[O_2Hb]$, Δ[HHb], and Δ[tHb], respectively; $\Delta[tHb] = \Delta[O_2Hb] + \Delta[HHb]$). [tHb] is linearly correlated to the cerebral blood volume (CBV) and exponentially to the CBF [Grubb et al., 1974]. In addition, changes in CBF and the cerebral metabolic rate of oxygen ($CMRO_2$) lead to opposite changes in $\Delta[O_2Hb]$ and Δ[HHb] [Wolf et al., 2002]. [O_2Hb], [HHb], and [tHb] are very sensitive to physiological changes, i.e., changes in temperature, metabolism, and brain activity due to neurovascular coupling. Several studies showed a high level of agreement between functional NIRS (fNIRS), functional magnetic resonance imaging (fMRI) [Kleinschmidt et al., 1996; Toronov et al., 2001a; Strangman et al., 2002], and PET [Hock et al., 1997; Villringer et al., 1997].

NIR and fNIR sensors can be built completely from optical parts, which make them insensitive to EMF. Thus, NIRS enables the investigation of potential immediate and long-lasting effects of EMF exposure on [O_2Hb], [HHb], and [tHb]. So far, immediate and long-lasting effects of GSM-EMF have been studied. Wolf et al. [2006] found small, borderline significant, and short-term changes in [O_2Hb] and [HHb], which corresponded to a decrease in CBF and CBV. No slow effect was found during 20 min of exposure. Curcio et al. [2009] found a significant linear increase in [HHb] during 40 min of exposure.

Since near-infrared light also penetrates superficial tissue, it provides simultaneous information on cerebral and superficial effects. Because longer source–detector distances probe deeper tissue layers, it is possible to estimate whether an effect is more likely to be superficial or cerebral [Okada et al., 1997].

NIRS signals also contain an oscillation corresponding to the heart rate (HR), which can be extracted. Of three published studies on the effects of GSM exposure on HR, two found no effect [Braune et al., 2002; Tahvanainen et al., 2004], while one showed a small reduction in HR [Huber et al., 2003]. No effects were found in two studies using UMTS exposure [Eltiti et al., 2007, 2009].

Despite the rapid replacement of GSM by UMTS, few exposure studies using UMTS signals exist, although effects of GSM on CBF and CBV were demonstrated. Thus, our aim was to investigate potential effects of UMTS-EMF using NIRS. Since previous studies using GSM-EMF indicated effects on different time scales [Wolf et al., 2006; Curcio et al., 2009], we analyzed two time scales. In addition, we studied subjective parameters and counting speed.

We tested the following hypotheses: (i) there is a significant short-term (within 80 s) effect of UMTS-EMF on [O_2Hb], [HHb], [tHb], and/or HR; (ii) there is a significant medium-term (80 s to 30 min) effect of UMTS-EMF on [O_2Hb], [HHb], [tHb], and/or HR; (iii) there is a dose-dependency of these effects; and (iv) there is an effect of UMTS-EMF on subjective parameters and counting speed. In addition, to set potential short-term changes in relation to normal brain activity, results were compared to a motor activation measurement.

MATERIALS AND METHODS

Subjects

Sixteen healthy, right-handed, male non-smokers (mean age ± standard deviation: 26.8 ± 3.9 years, weight: 83.2 ± 11.3 kg, height: 182.5 ± 8.8 cm, mobile phone use/day: 7.1 ± 4.5 min, years of mobile phone use: 8.4 ± 2.5 years) participated after giving written informed consent. The protocol was approved by the ethics committee of the Canton of Zurich. Subjects were asked to abstain from alcohol, medication and sports, and to maintain constant waking times, sleep hours, and coffee levels for each study day. Additionally, subjects had to switch off their mobile phone on the evening before the experiment to inhibit use on the measurement day. There were no withdrawals or drop-outs.

Study Design

Each subject encountered four different conditions on four different days at the same time of

day: (i) maximum peak SAR of 1.8 W/kg, (ii) maximum peak SAR of 0.18 W/kg, (iii) sham, and (iv) motor activation measurement. The three types of exposure took place on study days 1–3, in a controlled, randomized, crossover, and double-blind paradigm. On study day 4, a motor activation measurement was performed. Before each measurement, subjects answered a questionnaire about activities, tiredness, and well-being. Subjects were placed in a comfortable supine position. They were asked not to talk and to avoid movements during the measurement.

EMF Exposure or Sham Measurement

The measurement position T3 (Fig. 1A) for the sensor was chosen because this is a position close to where the mobile phone is usually held. Subjects had to insert earplugs to avoid potential external auditory stimuli, since position T3 was located close to the auditory cortex. Afterward, the center of the optical sensor was fixed at position T3 according to the international 10–20 EEG positioning system [Jasper, 1958]. Subjects counted back starting from 2000 during the whole measurement to ensure that subjects were mentally focused and did not fall asleep. To assess the counting, subjects reported the number reached after 12 min (triggered by an acoustic signal) and at the end of the measurement (*End_Exp*). A measurement consisted of 16 cycles, i.e., exposure segments of 20 s of UMTS-EMF exposure (ON) or sham were alternated with 60 s recoveries (OFF). Beforehand a baseline was recorded for 3 min, afterward for 6 min. A measurement lasted 31 min in total. Tiredness (Karolinska sleepiness scale [Akerstedt and Gillberg, 1990]), well-being (analog scale of 10 steps), and the subject's guess about the exposure condition was recorded after the measurement.

Motor Cortex Measurement

The sensor was placed 1.5 cm above the C3 position [Jasper, 1958] on the motor cortex for the motor activation experiment. This measurement had the same temporal structure as the exposure measurements, but subjects were actively finger tapping for 20 s instead of being exposed to UMTS-EMF.

Near-Infrared System

The commercially available ISS Oxiplex (ISS, Champaign, IL) is a frequency-domain NIRS instrument that employs 16 laser diodes at two wavelengths (eight at 690 nm and eight at 834 nm). It has two highly sensitive photomultiplier tubes as detectors. The light at the source is modulated with 100 MHz, and at the detector, the mean light intensity, amplitude of the intensity, and the phase shift (i.e., time of flight) is measured. To distinguish the light from the different light sources, these are time multiplexed. In its original state, the ISS Oxiplex is intended for measuring absolute concentrations of [O_2Hb], [HHb], and [tHb]. This requires a multidistance geometry with no spatial resolution. In addition, in this mode the instrument takes into consideration the relatively noisy phase shift and thus the instrument is insensitive to small changes in [O_2Hb], [HHb], and [tHb]. We adapted the ISS Oxiplex specifically for this study to achieve a higher spatial resolution and sensitivity. Modifications to hardware and software quadrupled the number of detector and light source combinations available for a single optical sensor to provide spatial information on

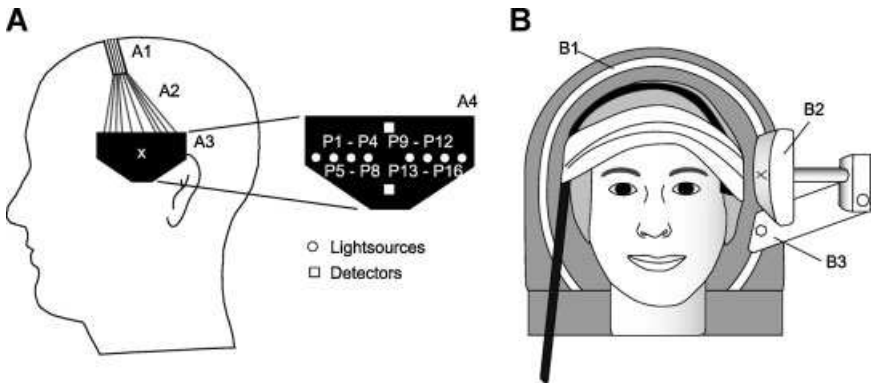


Fig. 1. **A**: Lateral view of sensor placement at the head. A1: 10 m-long bundle, A2: optical fibers, A3: optical sensor, and A4: sensor geometry with source and detector positions. All combinations of source and detector position were measured, which led to 16 paths (P1. . .P16) with separations between 1.7 and 3.4 cm. **B**: Frontal view of arrangement of patch antenna and subject's head. B1: track for the antenna slide, B2: patch antenna, and B3: antenna slide for positioning.

location and depth of concentration changes. In addition, by only including the light intensity signals, the instrument is highly sensitive to even small changes in [O_2Hb], [HHb], and [tHb]. The data acquisition rate was 25 Hz.

The optical NIR sensor was custom built without active metallic parts to be insensitive to UMTS-EMF. It consisted of two detectors and eight sources enabling 16 measurement paths (Fig. 1A). Each source position included light at two wavelengths (690 and 830 nm) to detect both [O_2Hb] and [HHb]. Ten-meter long glass fibers, again without metal parts, connected the sensor to the NIRS instrument, placed behind absorber walls in the measurement room to minimize potential electrical interference. During an interference test, it was proven that exposing the sensor to intermittent UMTS-EMF does not affect the measured signals, i.e., the NIRS setup is insensitive to UMTS-EMF.

UMTS Exposure System

The measurements were carried out in the basement of the University Hospital Zurich, Switzerland, where electromagnetic background was very low (at 1.9 GHz, the background electrical field strength was 0.0002 V/m). The bench for the subject was laterally shielded by pyramidal radiofrequency absorbers (ECCOSORB VHP-12, Emerson & Cuming, Randolph, MA), in order to minimize the possible UMTS-EMF reflexions of the exposure setup. The background EMF from 5 to 30 kHz at the experimental location was less than 90 nT and the only noticeable background EMF contributions are a GSM downlink signal in the 900 MHz band of 0.005 V/m, a frequency modulation (FM) radio signal at 88 MHz of 0.0005 V/m, and the hospital pager (at 451 MHz) with an electrical field strength of 0.0003 V/m.

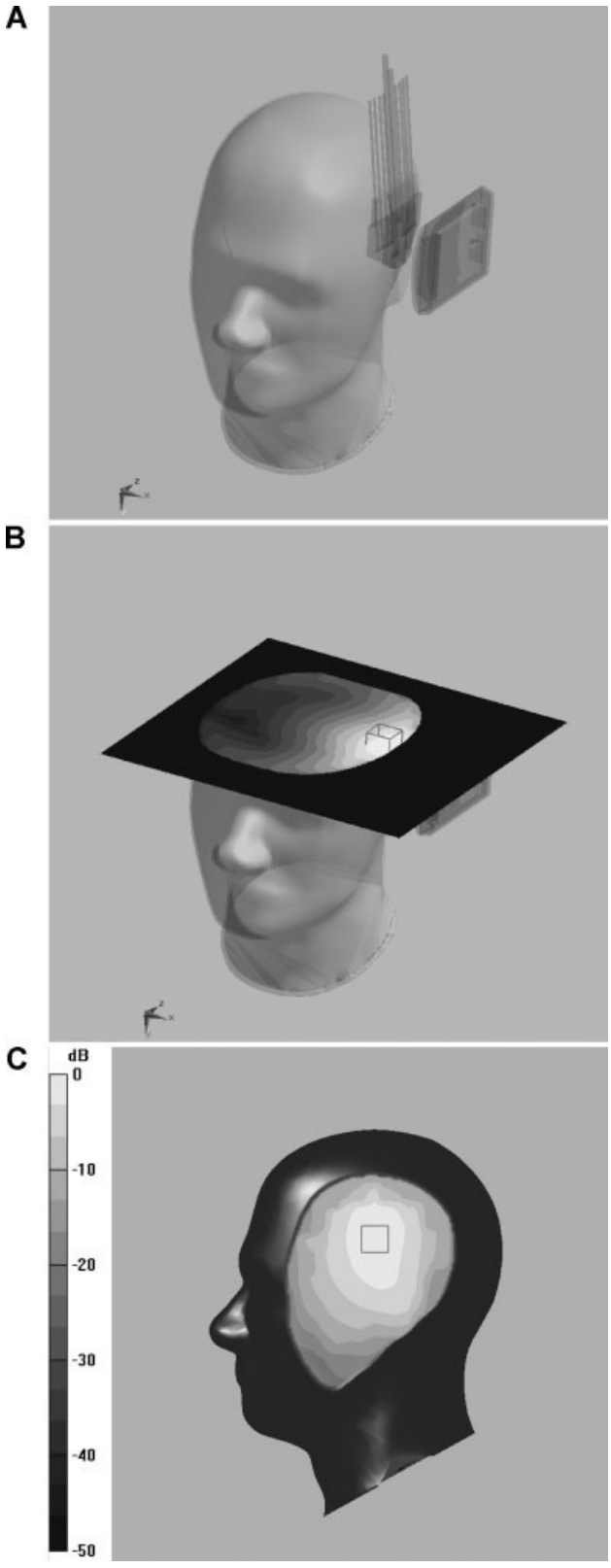
The signal generator (SMIQ 03B, Rhode & Schwarz, Munich, Germany), power amplifier (RCS 1900 amplifier, 20 W, Swisscom, Worblaufen, Switzerland), couplers and switching matrixes required to generate UMTS-EMF, as well as the control laptop were located outside the exposure chamber. UMTS-EMF was transmitted to the subject's head by a planar patch antenna (SPA 2000/80/8/0/V, Huber & Suhner, Pfäffikon, Switzerland), centered on T3 at a distance of 4 cm to the head (Fig. 1B). This led to a homogenous specific absorption rate (SAR) distribution over the measurement area and left space for the NIR sensor (Fig. 2). The patch antenna emitted a wideband code division multiple access (W-CDMA) downlink signal [Zwamborn et al., 2003] with a carrier frequency of 1.9 GHz, similar to a base station. Three different exposure conditions were utilized: (i) sham (maximum peak SAR over 10 g at 0.0 W/kg), (ii) low dose (maximum peak SAR over 10 g at 0.18 W/kg), and (iii) high dose (maximum peak SAR over 10 g at 1.8 W/kg). The SAR value of the high-dose condition was below the SAR limit given by the International Commission on Non-Ionizing Radiation Protection (ICNIRP) [ICNIRP, 1998].

To evaluate SAR distribution in the human head, numerical dosimetry was performed using SEMCAD X (Version 13, Schmid and Partner Engineering, Zurich, Switzerland). The Specific Anthropomorphic Mannequin (SAM) phantom defined in CENELEC 50361 [CENELEC, 2001] was used for the simulation of the spatial peak SAR over 10 g generated by the setup. The simulations were verified by an experimental SAR evaluation with the DASY5 Dosimetric Assessment System (Schmid and Partner Engineering) at the IT'IS Foundation in Zurich. The simulated and experimental data showed a high agreement (deviations smaller than $\pm 5\%$).

The type of signal (downlink) and measurement position (T3) were selected based on an exploratory study (EP), where potential effects of four different UMTS signals (continuous wave, downlink signal, W-CDMA uplink with one communication channel, and W-CDMA uplink with six communication channels [Ndoumbé Mbonjo Mbonjo et al., 2004]) were studied in eight subjects. The center of the antenna and sensor were located at two positions, T3 and C3, the motor cortex. The first corresponds to the closest position to the ear accessible with the optical sensor and the latter represents the middle point, where Huber et al. [2005] found an effect on the rCBF and the motor cortex. For all four UMTS signals, a maximum peak SAR value over 10 g of 1.8 W/kg was applied.

The EP was carried out to investigate potential short-term effects of intermittent UMTS-EMF on [O_2Hb], [HHb], and [tHb] and to define the protocol for the main study presented in this paper. The difference between the last 10 s of exposure and the last 10 s before exposure was calculated and modeled using a linear mixed-effects model depended on the signal type, exposure position, measurement path, and exposure segment. No statistically significant short-term effect was found for any UMTS-EMF signal and measurement position. For position T3 and the downlink signal, changes in [O_2Hb], [HHb], and [tHb] were greatest and, therefore, selected for the current study.

The exposure system was controlled by software written in LabView 7 (National Instruments, Austin, TX). The software ran in two modes, open



mode for testing purposes and random mode for controlled, randomized, crossover, and double-blind studies. In random mode, the exposure conditions (sham, low dose, and high dose) were automatically randomized by computer for each subject. The exposure condition and forward and reverse UMTS-EMF power were encrypted. A password-encoded program deblinded the conditions after data analysis was completed.

NIRS Data Analysis

Optical intensity data were converted to [O_2Hb], [HHb], and [tHb] changes by the widely used, modified Beer–Lambert law [Wray et al., 1988; Matcher et al., 1995]. In short, the conventional Beer–Lambert law is only valid in objects without light scattering and describes an exponential relationship between light transmission through an object and the concentration of an absorber in the object. The modified Beer–Lambert is valid for objects that are strongly scattering, e.g., tissue. It fulfils the diffusion approximation of light transport through tissue. It adjusts for the increased pathlength of light due to scattering by introducing the differential pathlength factor (DPF) and enables the conversion of changes in intensity to changes in [O_2Hb], [HHb], and [tHb]. DPF values have been measured and published [Zhao et al., 2002] and accordingly we used a $DPF_{690nm} = 8.21$ and $DPF_{830nm} = 7.3$.

Short-Term: [O_2Hb], [HHb], and [tHb]

Movement artifacts (MA) in Δ[O_2Hb] and Δ[HHb] were reduced according to Scholkmann et al. [2010]. The method uses a moving standard deviation to detect artifacts, and a spline interpolation to remove them. The moving window length of the standard deviation was adjusted manually for each data set to remove MAs most effectively. The algorithm significantly reduced MAs and improved the signal quality, but not all MAs were removed completely.

The MA-reduced Δ[O_2Hb] and Δ[HHb] were band-pass filtered (0.008–0.4 Hz). The number of sampling points was reduced to a final sampling frequency of 1 Hz. Ten data points were smoothed and each exposure/stimulation segment was linearly detrended.

Fig. 2. **A**: SAM phantom model with optical sensor placed at T3 and the patch antenna at a distance of 4 cm to the head surface. **B,C**: SAR distributions through cross-sections with the maximum spatial peak SAR averaged over 10 g. The cube marks the location of the maximum peak SAR values (1.8 W/kg over 10 g for the high dose and 0.18 W/kg over 10 g for the low dose).

To identify the remaining MAs, all data were visually inspected for MAs. Segments containing MAs and exposure segment 8, where the subject reported the number reached in the counting task, were removed from further analysis (17.9% of segments for $\Delta[O_2Hb]$ and 17.4% for Δ[HHb]). For all paths and measurements, at least 8 segments contained no MAs.

For each path a block average over the remaining segments was calculated for $\Delta[O_2Hb]$ and Δ[HHb]. The sum of $\Delta[O_2Hb]$ and Δ[HHb] yielded Δ[tHb]. A mean over 10 s was calculated for $\Delta[O_2Hb]$, Δ[HHb], and Δ[tHb] and used as input for the statistics.

Short-Term: Heart Rate

The NIRS instrument has a high time resolution of 25 Hz that, like in pulse oximetry, enables the detection of the pulsewave, i.e., changes in $[O_2Hb]$ and [HHb] due to systole (higher concentration of both) and diastole (lower concentration), which reflects the heart beat and enables the extraction of the HR. The HR was calculated from intensity data. The optical path with the highest signal to noise ratio, i.e., the highest ratio between the power in the HR band (0.7–1.4 Hz) and noise-band (5–5.7 Hz), was selected for the fast Fourier transform (FFT). Each exposure segment was divided into eight 10 s-long segments. To enhance the accuracy of the FFT, the precise period was adjusted at the beginning and end to exclude incomplete heart beats. For this purpose heart beats were assessed by detecting the maxima of the intensity data, which is similar to the algorithms used in pulse oximetry. The HR was then calculated using FFT with a resolution of 0.08 Hz. For the HR of this optical path, a block average was calculated and used as input for the statistics.

Medium-Term: $[O_2Hb]$, [HHb], and [tHb]

$\Delta[O_2Hb]$ and Δ[HHb] were low-pass filtered (cut-off frequency: 0.0125 Hz). A mean was calculated over every exposure segment (80 s), except for the 8th segment where the subject reported the number reached. Additionally, the baseline was divided into 80 s segments: two before the first exposure segment and four after the last one. All segments were baseline corrected by subtracting the mean of the first segment.

MAs may have a considerable influence on the mean values of segments and hence also on the medium-term analysis. To reduce MAs, they were detected for each path by calculating the concentration change between two segments. Changes exceeding three standard deviations were defined as artifacts and were set to the mean difference between segments. The following segments were shifted accordingly.

The algorithm was performed repeatedly until no more MAs were found (twice for $\Delta[O_2Hb]$ and three times for Δ[HHb]). 0.72% of all segments were corrected for $\Delta[O_2Hb]$, and 0.98% for Δ[HHb]. Δ[tHb] was calculated from the corrected $\Delta[O_2Hb]$ and Δ[HHb].

Medium-Term: Heart Rate

The HR was calculated for the same time segments as described previously and an FFT was applied to determine HR. The changes in the HR were calculated by subtracting the HR of the first segment.

Counting and Self-Evaluations

The difference between subjective tiredness (*T*) and well-being (*S*) before and after measurements was calculated and named *Exp_T* and *Exp_S*, respectively. The number reached at the beginning of the 8th exposure segment (*Mid_Exp*) and the number reached at the end of the measurement (*End_Exp*) was recorded by the experimenter, respectively, for each subject.

Statistical Analysis

The statistical analysis was carried out using the statistical software R [R Development Core Team, 2009] and a P-value < 0.05 indicated significance. Exposure conditions were not deblinded until data analysis was completed. Thus, all exposure conditions were analyzed in the same way and bias by the experimenter can be excluded.

Linear mixed-effects models (procedure 1me in the R statistical software), a statistical term that any statistician will understand, were applied to changes in measurement variables to test the influence of all known factors (time (*Time*), exposure condition (*Exposure*), and measurement path (*Path*)) and known covariables (*HR*, *Exp_T*, *Exp_S*, *Age*, *Weight*, *Height*, *Health*, caffeine on measurement day (*Caffeine*), daytime of measurement (*Meas_time*), time awake (*Time_awake*), hours of sleep the night before (*Sleep_h*), EMF perception (*EMF_perception*), EMF hypersensitivity (*EHS*), number reached mid-experiment (*Mid_Exp*), and number reached at the end of experiment (*End_Exp*)); the interactions between *Exposure*, *Path*, and *Time* were also considered. A step-wise exclusion procedure based on Akaike's Information Criterion (AIC) [Akaike, 1973] was

performed to determine which variables had a significant influence. For all linear mixed-effects models, a residue analysis was performed to check its validity. The influence of the subjects was considered as a random factor.

If the factor *Exposure* was significant, a multiple comparison of means using the Tukey correction (procedure TukeyHSD in the R statistical software) was applied to determine the differences between exposure types. Additionally, for all time points we calculated the mean effect and 99% confidence interval, and performed a multiple comparison of means with the Tukey correction to test for significant differences between the exposure types.

Potential short-term effects were compared to motor activation. For the motor cortex only the size of the effect was of interest, hence it was modeled (procedure 1me in the R statistical software) in dependency of the predictor *Time*. Only subjects showing a significant activation (14 of 16 for [O_2Hb], 12 of 16 for [HHb], and 14 of 16 for [tHb]) were considered in the model. To enable direct comparison between exposure and motor activation measurements, data were analyzed and modeled the same way. This means that for the motor activation, not only the paths showing an activation but all paths were included in the model. This led to lower mean effects than the values found in the literature. For this reason, we also stated the maximal change elicited by the activation, which were comparable to literature values.

Counting and Self-Evaluations

Self-evaluations and counted numbers were used as predictors for concentration changes and were also estimated by their own mixed-model because well-being and tiredness change during measurement and the influences on counting speed could affect the cerebral oxygenation, and these variables may depend on several monitored variables such as time awake.

The reporting of *Mid_Exp* was used to test the subject's counting and thus was only a predictor. *End_Exp*, *Exp_T*, and *Exp_S* were viewed as speed measures and were estimated by a linear mixed-effects model. The analysis of *Exp_S* was discarded because most of the subjects reported no difference in well-being before and after the measurement. Only in 4 out of 48 measurements (2 sham, 1 low, and 1 high-dose exposure) did subjects report that they experienced EMF. These occurrences were distributed in a random pattern over the exposure conditions and subjects, and no statistical method can be applied due to the low number of occurrences.

Responder Analysis

To test for responders at an individual level, the last 10 s of UMTS on and off for each exposure segment without MAs were compared with a paired Wilcoxon signed-rank test over one measurement path. The number of significant paths per exposure condition and subject was calculated, and the number of occurrences per exposure condition was compared within each subject.

RESULTS

Short-Term

After the step-wise exclusion procedure based on the AIC criteria, which removed all variables without relevant effect on the dependent variables, the following variables with significant influence remained for the short-term analysis:

$$\begin{aligned}\Delta[O_2Hb] &\sim \text{Time} + \text{Exposure} + \text{Time:Exposure}\\ \Delta[\text{HHb}] &\sim \text{Time} + \text{Exposure} + \text{Time:Exposure}\\ \Delta[\text{tHb}] &\sim \text{Time} + \text{Exposure} + \text{Time:Exposure}\end{aligned} \quad (1)$$

This means, for example, that for the dependent variable $\Delta[O_2Hb]$, a significant effect ($\sim$) of the factors Time and Exposure as well as the interaction (:) of Time and Exposure was found.

For ΔHR no significant dependency on any factor was found; results are included in Table 1. Graphs are shown in Figure 3A; for graphs with 99% confidence interval at each time point, please refer to the supplementary information available from the online version of this journal. The asterisks mark significant differences ($P < 0.01$) compared to sham. Mean effects and confidence intervals at 40 s are included in Table 2.

To account for negative responses during motor stimulation, not only the mean effect but also the mean of the absolute effects was calculated as a measure of changes induced by the activation (Table 2). The maximum response in a single path was 0.567 μM $\Delta[O_2Hb]$, 0.251 μM Δ[HHb], and 0.610 μM Δ[tHb], and the minimum response was -0.245 μM for $\Delta[O_2Hb]$, -0.110 μM for Δ[HHb], and -0.355 μM for Δ[tHb].

The mean effect of the exposures at 40 s was compared to the motor activation and confidence intervals calculated with error propagation according to Doerffel [1984] (Table 2). These values are an upper limit for the estimation because the mean response over all paths during motor stimulation was calculated independent of an activation.

TABLE 1. Short-Term Analysis: *F*- and *P*-Values for the Different Linear Mixed-Effects Models* (Procedure 1me in the R Statistical Software) of Δ[O_2Hb], Δ[HHb], and Δ[tHb].

Variable	Factors	Number of degrees of freedom (numDF)	$F_{\text{numDF,denDF=6105}}$	*P*-Value
Δ[HHb]	Time	7	15.06	<0.001
	Exposure	2	10.11	<0.001
	Time:Exposure	14	7.00	<0.001
Δ[O_2Hb]	Time	7	19.43	<0.001
	Exposure	2	42.11	<0.001
	Time:Exposure	14	15.24	<0.001
Δ[tHb]	Time	7	14.25	<0.001
	Exposure	2	41.71	<0.001
	Time:Exposure	14	14.42	<0.001

*A statistical term that any statistician will understand.

The multiple comparisons of means with the Tukey correction between exposures for each path revealed no significant differences. This means that no regional effects were found.

Medium-Term

After the step-wise exclusion procedure, the following variables with significant influence remained for the medium-term analysis:

$$\begin{aligned}
&\Delta[O_2Hb] \sim \text{Time} + \text{Exposure} + \text{Path} + \text{HR} + \text{Exp_T} + \text{Exp_S} + \text{Time_awake} + \text{Sleep_h} + \ldots \\
&\quad \text{Mid_Exp} + \text{End_Exp} + \text{Exposure:Path} \\
&\Delta[\text{HHb}] \sim \text{Time} + \text{Exposure} + \text{Path} + \text{HR} + \text{Exp_T} + \text{Exp_S} + \text{Meas_time} + \text{Sleep_h} + \ldots \\
&\quad \text{End_Exp} + \text{Exposure:Path} \\
&\Delta[\text{tHb}] \sim \text{Time} + \text{Exposure} + \text{Path} + \text{HR} + \text{Exp_S} + \text{Meas_Time} + \text{End_Exp} + \text{Exposure:Path} \\
&\Delta\text{HR} \sim \text{Time} + \text{Exposure} + \text{Exp_S} + \text{Time_awake} + \text{Mid_Exp} + \text{End_Exp}
\end{aligned} \tag{2}$$

In contrast to the short-term analysis, the medium-term ΔHR showed a significant dependency on several predictors and was thus modeled analogously to Δ[O_2Hb], Δ[HHb], and Δ[tHb]. *F*- and *P*-values for the factors of the different mixed-effects models are included in Table 3.

A multiple comparison of means with the Tukey correction was performed and we found the following significant mean differences (99% confidence intervals) between sham and exposures: Δ[O_2Hb] (sham, 0.18 W/kg) = 0.78 (0.43, 1.12) μM ($P < 0.001$); Δ[HHb] (sham, 0.18 W/kg) = − 0.16 (−0.30, −0.03) μM ($P = 0.001$); Δ[HHb] (sham, 1. 8 W/kg) = − 0.20 (−0.34, −0.06) μM ($P < 0.001$); and Δ[tHb] (sham, 0.18 W/kg) = 0.70 (0.34, 1.05) μM ($P < 0.01$). For ΔHR the difference between sham and 1.8 W/kg of 1.84 bpm (1.16, 2.52) was significant ($P < 0.001$).

Graphs with mean effects for Δ[O_2Hb], Δ[HHb], and Δ[tHb] are shown in Figure 3, and for ΔHR in Figure 4. The asterisks mark significant differences ($P < 0.01$) compared to sham. For graphs with 99% confidence interval at each time point, please refer to the supplementary information available from the online version of this journal.

During the analysis and before deblinding, six relevant outlying traces (out of 768) were identified (2 sham, 3 low dose, and 1 high-dose exposure). Since there was no reason to consider these traces as artifacts, we decided to perform the statistical analysis with and without them to investigate their influence on the results.

Without the outliers, the factor *Exposure* was no longer significant for Δ[O_2Hb] and Δ[tHb]. For Δ[HHb] a multiple comparison of means with the Tukey correction showed significant mean differences between sham and exposures: Δ[HHb] (sham, 0.18 W/kg) = − 0.14 (−0.28, −0.006) μM ($P = 0.007$) and Δ[HHb] (sham, 1.8 W/kg) = − 0.19 (−0.33, −0.05) μM ($P < 0.001$). Remarkably, the number of significant time points increased for Δ[HHb] for 1.8 W/kg exposure. The number of significant time points stayed approximately the same for Δ[O_2Hb] and Δ[tHb]. The results so far refer to differences between exposure conditions.

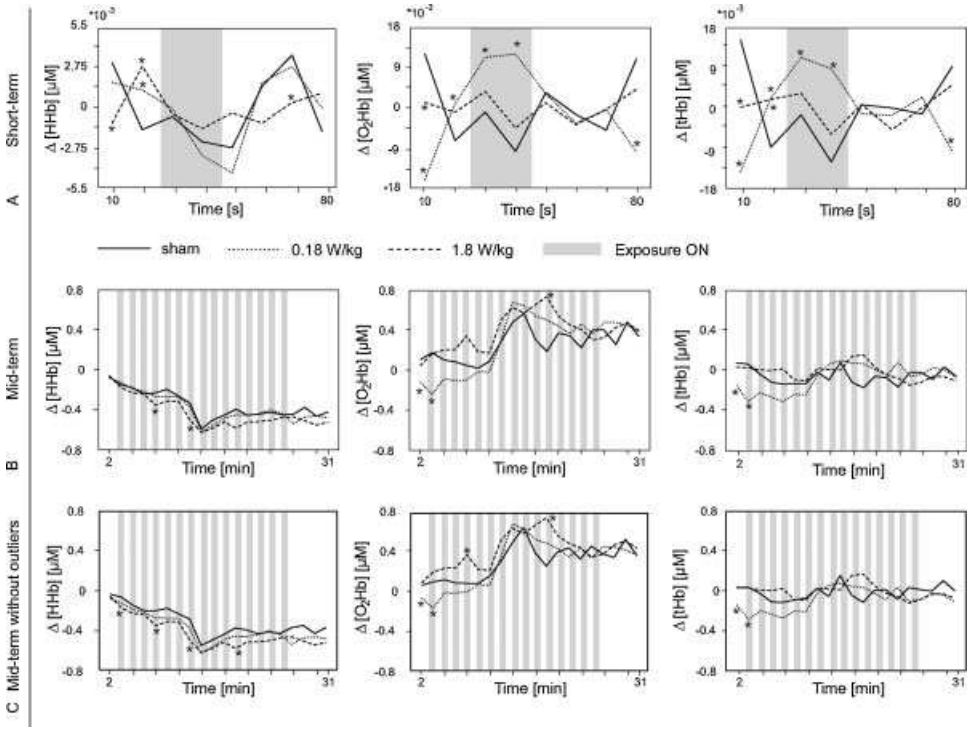


Fig. 3. Time-evolution of mean effects for $\Delta[O_2Hb]$, $\Delta[HHb]$, and $\Delta[tHb]$ for the different exposures for the short-term (**A**), medium-term (**B**), and the medium-term without outliers (**C**). Significant results ($P < 0.01$) comparing 0.18 or 1.8 W/kg to sham are marked with an asterisk beneath the corresponding mean effect.

Independent of exposure condition, [HHb] decreased, $[O_2Hb]$ increased, and [tHb] was unchanged over time. For the sham condition in three out of four sensor quadrants, the mean effect for $\Delta[O_2Hb]$ and ΔtHb at the last time point was significantly higher for the shortest source–detector distances than for the longest source–detector distances. This indicates that the trend during the measurement, which was observed for all conditions, has its origin in superficial changes.

Counting and Self-Evaluations

The linear mixed-effects analysis for *End_Exp* and *Exp_T* showed no significant dependence on any predictor.

Responder Analysis

We did not find any difference between the exposure conditions for any of the subjects. Over all subjects, the total number of significant paths

TABLE 2. Short-Term Analysis of the Mean Effects of $\Delta[O_2Hb]$, $\Delta[HHb]$, and $\Delta[tHb]$. A: Mean Effect and Estimated Confidence Interval (0.5%, 99.5%) in μM for $\Delta[O_2Hb]$, $\Delta[HHb]$, and $\Delta[tHb]$ at 40 s for All Measurement Conditions. B: Mean Effect of Exposure for $\Delta[O_2Hb]$, $\Delta[HHb]$, and $\Delta[tHb]$ at 40 s Compared to the Motor Activation, Given in Percent.

		$\Delta[O_2Hb]$		$\Delta[HHb]$		$\Delta[tHb]$	
Condition	Unit	Mean effect	CI (0.5%, 99.5%)	Mean effect	CI (0.5%, 99.5%)	Mean effect	CI (0.5%, 99.5%)
A							
Sham	μM	−0.011	(−0.017, −0.004)	−0.003	(−0.005, −0.001)	−0.013	(−0.020, −0.006)
0.18 W/kg	μM	0.013	(0.006, 0.02)	−0.004	(−0.006, −0.001)	0.010	(0.002, 0.017)
1.8 W/kg	μM	−0.005	(−0.012, 0.002)	−0.002	(−0.004, 0.001)	−0.007	(−0.014, 0.001)
Motor cortex	μM	0.072	(0.086, 0.100)	−0.011	(−0.0114, −0.0106)	0.077	(0.062, 0.092)
Motor cortex abs (effect)	μM	0.126	(0.113, 0.139)	−0.022	(−0.025, −0.019)	0.118	(0.104, 0.132)
B							
0.18 W/kg versus motor cortex	%	17.4	(−60.2, 94.9)	5.3	(−1109.1, 1119.6)	17.3	(−70.6, 105.1)
1.8 W/kg versus motor cortex	%	4.2	(−70.2, 78.6)	−5.0	(−1118.9, 1109.0)	5.1	(−79.4, 89.6)

TABLE 3. Medium-Term Analysis: *F*- and *P*-Values for All Factors of the Different Linear Mixed-Effects Models* (Procedure 1me in the R Statistical Software) of Δ[O_2Hb], Δ[HHb], and Δ[tHb]. For Each Covariable, the Influence Column Indicates the Direction of Influence of the Measurement Variable

Variable	Factors	Number of degrees of freedom (numDF)	Influence	$F_{numDF, denDF}$	*P*-Value
Δ[HHb] (denDF = 14952)	Time	19		73.49	<0.001
	Exposure	2		9.88	<0.001
	Path	15		76.68	<0.001
	Exposure:Path	30		7.79	<0.001
	HR	1	−	654.22	<0.001
	Exp_T	1	−	528.84	<0.001
	Exp_S	1	−	21.10	<0.001
	Time_waking	1	−	53.53	<0.001
	Sleep_h	1	−	91.53	<0.001
	End_Exp	1	+	472.59	<0.001
Δ[O_2Hb] (denDF = 14954)	Time	19		18.22	<0.001
	Exposure	2		26.44	<0.001
	Path	15		53.68	<0.001
	Exposure:Path	30		7.37	<0.001
	HR	1	+	134.09	<0.001
	Exp_T	1	+	52.21	<0.001
	Exp_S	1	+	229.74	<0.001
	Time_waking	1	+	86.24	<0.001
	Sleep_h	1	+	20.11	<0.001
	Mid_Exp	1	+	56.91	<0.001
	End_Exp	1	−	7.60	<0.001
Δ[tHb] (denDF = 14954)	Time	19		1.62	0.042
	Exposure	2		20.81	<0.001
	Path	15		76.45	<0.001
	Exposure:Path	30		6.84	<0.001
	HR	1	+	27.87	<0.001
	Exp_S	1	+	251.88	<0.001
	Meas_Time	1	−	158.44	<0.001
	End_Exp	1	+	215.33	<0.001
ΔHR (denDF = 899)	Time	20		3.47	<0.001
	Exposure	2		24.72	<0.001
	Exp_S	1	−	3.96	0.047
	Time_waking	1	−	5.23	0.022
	Mid_Exp	1	+	131.13	<0.001
	End_Exp	1	−	44.64	<0.001

*A statistical term that any statistician will understand.

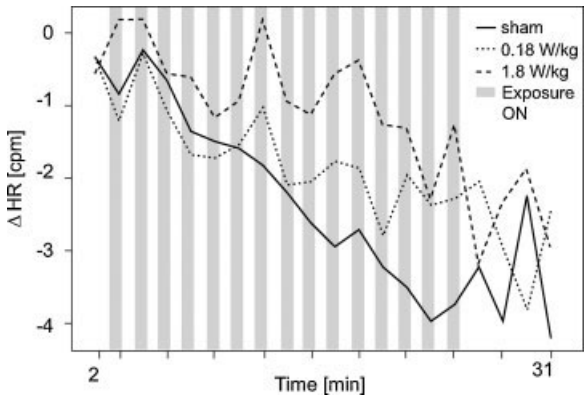


Fig. 4. Time-evolution of mean effects for the medium-term ΔHR displayed for the different exposures. No significant results ($P < 0.01$) comparing 0.18 or 1.8 W/kg to sham were found for single time points.

was close to the 5% of stochastically expected significances.

DISCUSSION

Short-Term Changes

We found a significant short-term response of Δ[O_2Hb], Δ[HHb], and Δ[tHb], which were significantly influenced by the factors *Time*, *Exposure*, and the interaction *Time:Exposure* (Table 1). This interaction indicates that the concentration changes during the different exposure conditions vary significantly over time (Fig. 3A). All time series were detrended in the analysis and thus have a mean over time equal to zero. This ensures that the variance between subjects is similar, and different from zero, at every time

point during the measurement. Another option is to set the last value before exposure to zero for all subjects. In this case the variance at this time point is equal to zero, which is statistically problematic. The detrending leads to an equilibrium of positive and negative concentration changes and thus it explains the values, which were significantly different from zero before the exposure. Detrending represents the more conservative estimate of potential effects.

In a comparison of means between the exposures, significant differences were obtained for several time points (Fig. 3A). For the high dose, [O_2Hb] and [tHb] are significantly lower than in the sham condition for the first 10 s or first 20 s (Fig. 3A) and [HHb] is significantly different for the first 20 s and at 70 s. This can be explained by the high [O_2Hb] and [tHb] values at 10 s in the sham condition, which contributes to the significance for the high dose. For [HHb], it is noteworthy that the amplitude of changes during sham exposure is similar to the amplitude during EMF exposure. This may indicate spurious changes. For the low dose, [O_2Hb] and [tHb] are significantly higher during exposure than in sham condition and [O_2Hb] and [tHb] are significantly lower for the first and last 10 s. This pattern during exposure may indicate increased blood flow, as described by Hoshi et al. [2001]. The low [O_2Hb] and [tHb] values at 10 s seem to imply that the increase starts before the exposure onset. However, it has to be kept in mind that the value at 80 s is connected to the value at 10 s because exposure was repeated. This could be interpreted as an increase during exposure and a decrease after exposure, which recovers to baseline levels only at 20 s. For the sham condition for [O_2Hb] and [tHb], the change between the first and second time point is relatively high compared to the other concentration changes. This high concentration change in the sham exposure may indicate a spurious effect.

The pattern of short-term results (no effect at the high dose and an effect at the low dose) and the results of the EP (no effect at the high dose for all signal types and measurement positions) indicate that there may also be short-term effects for the other UMTS signal types used in the EP at the lower dose.

Although some signs for spurious effects or coincidences are present, it has to be kept in mind that the probability of such effects is low ($<1\%$). The comparison with the amplitude of the motor response showed that the short-term effects are small ($\approx 17\%$ for [O_2Hb] and [tHb]). The effects did not show any regional dependency.

To the best of our knowledge, the only study investigating short-term effects of intermittent EMF was performed by our group [Wolf et al., 2006]. A decrease in blood flow was found with a lower significance level. The study was not comparable due to the different carrier frequency, modulation, SAR value, and exposure protocol (2 s on followed by 2 s off for 20 s instead of 20 s on) and the interference present during the 2 s of exposure.

For the presented short-term effects, a purely thermal effect is unlikely because thermal effects are expected to show a proportional dependency on the field intensity. The results indicate that this is not the case. It is also possible that the non-linear dependency on the field intensity is caused by two interfering effects showing a linear dose-dependency, but with opposite signs.

In summary, our results suggest a short-term effect of UMTS-EMF, whose amplitude is quite small compared to the response to a functional activation ($\approx 17\%$ for [O_2Hb] and [tHb]).

Medium-Term Changes

ΔHR decreased with time for all exposure conditions because the subjects relaxed in a supine position (Fig. 4). We found a significant difference in ΔHR between sham and the high dose of 1.84 bpm (1.16, 2.52), taking into account all time points. This increased HR indicates that the subjects relaxed less. A GSM study by Huber et al. [2003] showed a reduction in HR during waking and stage 1 sleep, whereas, Braune et al. [2002] and Tahvanainen et al. [2004] found no effect of GSM-EMF on the HR in randomized crossover trials. In contrast to our results, Eltiti et al. [2007, 2009] did not find an effect on HR using a base station-like UMTS signal, which had a different carrier frequency of 2020 MHz and was continuous. Based on the literature cited, we conclude that the possible influence of RF exposure on the HR is still unclear.

During the measurement, [O_2Hb] increased, [HHb] decreased, and [tHb] remained stable, independent of the exposure condition. These findings agree with Wolf et al. [2006], but disagree with Curcio et al. [2009], who found a decrease in [O_2Hb] and an increase in [HHb]. The analysis indicated that these changes represent a superficial increase in blood flow. One likely explanation is that the temperature below the sensor on the head increased due to the shielding of skin from ambient air and thus superficial blood flow increased. Another explanation is that the pressure exerted by the sensor on the skin initially inhibited blood flow. This may have induced physiological reactions to increase blood flow. However, these potential confounders affected all exposure conditions in the same way.

Since the outliers influence the medium-term results of [O_2Hb] and [tHb] significantly, there is some uncertainty in our interpretation. The number of outliers per exposure indicates that they are not due to EMF effects but more likely due to non-identified artifacts, and thus we think that the analysis without these six outliers is more trustworthy. The significant difference in [O_2Hb] and [tHb] was only found for the analysis including the outliers and it disappeared when the outliers were removed. Thus, we think that this effect is spurious. The analysis without outliers at each time point revealed several significances: Δ[O_2Hb] and Δ[tHb] were significant for the low dose at the first 4 min, even before the exposure started and hence indicate spurious effects; both significances for Δ[O_2Hb] of the high dose seem to be distributed over time in a random manner with no clusters formed at any time point.

Independent of the analysis, Δ[HHb] was significantly lower for both exposures compared to sham, with a slightly larger effect for the higher dose. The analysis without outliers at each time point revealed several significances distributed over time and forming no clusters. However, the effect is always a decrease in Δ[HHb] and is supported by the significant decrease of Δ[HHb], taking into account all time points. This effect can be interpreted as a decrease in oxygen consumption. No dependencies on the light path and thus no regional effects were observed.

Wolf et al. [2006] found no significant difference in [HHb] between sham and GSM exposure, whereas, Curcio et al. [2009] presented a significant increase in [HHb] over time for the GSM exposure. These differences may be explained by different exposure types, doses, and times. Three PET studies using GSM-EMF showed an increase in rCBF [Huber et al., 2005; Aalto et al., 2006] and one showed a decrease, which was interpreted as a spurious auditory effect [Haarala et al., 2003]. Thus, for GSM an increase of rCBF is likely. For UMTS-EMF only one study was performed, which observed no change in rCBF [Mizuno et al., 2009], in agreement with our results.

Counting and Self-Evaluations

We found no significant dependence on the exposure condition for the increase in tiredness during the measurement (*Exp_T*). This corresponds to Koivisto et al. [2001] and Rubin et al. [2006], who employed GSM-EMF. Besides the EMF type, the studies had different study designs. Koivisto et al. [2001] assessed tiredness and other subjective measures only in relation to the exposure conditions and neglected the influence of sleeping hours, time awake, coffee level, and similar factors. Rubin et al. [2006] assessed subjective measures such as tiredness 24 h after the exposure session and not directly after the measurement.

We also found no significant dependence of the counted number on the exposure condition. To the best of our knowledge no similar study has been performed.

Limitations

The current study applied a W-CDMA downlink signal at 1.9 GHz in repetitive cycles to assess potential alterations in blood circulation. The study was carried out with a homogenous population to minimize inter-individual variations and to enhance sensitivity to detect potential effects. The results cannot be transferred to other demographics.

The penetration depth of a near-infrared light bundle (i.e., the path of those photons from a source that reaches the detector) depends on the source–detector distance and the optical properties of the tissue. For a tissue with a typical $\mu_a = 0.1\ cm^{-1}$ and $\mu_s' = 8\ cm^{-1}$, the mean penetration depth at a source–detector distance of 1.5 and 3.5 cm is 0.5 and 0.8 cm, respectively. This means that half of the photons travel deeper and thus brain activity from a depth of 2.5 cm was detected [Toronov et al., 2001a]. Since shorter source–detector distances have a lower penetration depth than longer ones and because we have simultaneously measured at different distances in our setup, in principle our data contain depth information about concentration changes. However, since near-infrared light is highly scattered in human tissue, in practice it was not possible to extract this depth information with a reasonable quantitative accuracy. It is qualitatively possible to distinguish whether an effect is deep or superficial by looking at the concentration changes at the different light paths; for example, if the concentration change is higher for bundles with a longer source–detector distance, the signal originates from a deep layer of tissue or vice versa.

The high temporal resolution and the unique insensitivity to EMF enable continuous measurements and a high flexibility in the choice of exposure sequences. NIRS is so far the only technique to study short-term effects during EMF exposure.

Future Studies

In future studies, the current study should first be reproduced independently. It should also be tested

whether similar effects can be found in other populations, e.g., different ages and females. In addition, different types of signals should be used, e.g., handset-like signals or continuous wave signals. This may give information about the underlying mechanisms. Furthermore, by having more power levels, it would be possible to describe the dose–response curve in more detail.

CONCLUSION

For the first time, a NIRS instrument inert to EMF enabled the measurement of potential effects of intermittent UMTS-EMF exposure. In summary, based on our hypotheses we found: (i) a significant short-term response of [O_2Hb] and [tHb] to the low-dose UMTS-EMF exposure within 80 s, which is small ($\approx$17%) compared to a functional activation; (ii) a significant medium-term response of [HHb] to the low and high-dose UMTS-EMF exposure, which is in the range of normal physiological fluctuations, and a medium-term response of the HR to the high-dose UMTS-EMF exposure within 80 s to 30 min; and (iii) no significant dependence between the self-evaluation and UMTS-EMF exposure, and counting speed and UMTS-EMF exposure.

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